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Clinical pharmacology and therapeutic drug monitoring of first-line anti-tuberculosis drugs

Sturkenboom, Marieke Gemma Geertruida

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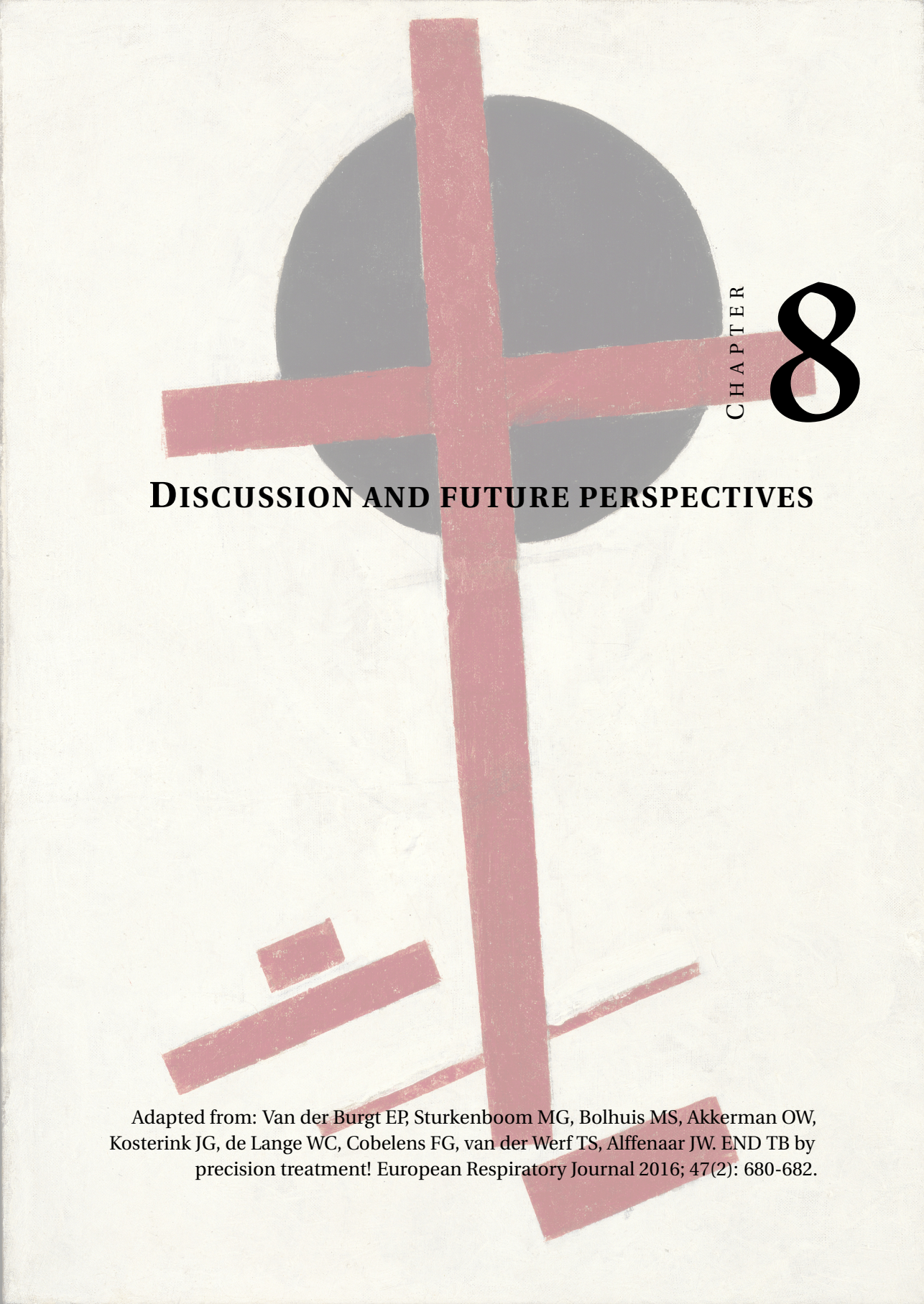
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CHAPTER

8

DISCUSSION AND FUTURE PERSPECTIVES

Adapted from: Van der Burgt EP, Sturkenboom MG, Bolhuis MS, Akkerman OW, Kosterink JG, de Lange WC, Cobelens FG, van der Werf TS, Alffenaar JW. END TB by precision treatment! *European Respiratory Journal* 2016; 47(2): 680-682.

Treatment of tuberculosis (TB) with the four first-line drugs, though usually successful, has been challenged by the emergence of drug resistance, toxicity, relapse and non-response [1]. In this thesis, we have identified factors that can be optimized in the first-line treatment of drug-susceptible TB. In Chapters 3 and 4, two of the prerequisites for therapeutic drug monitoring (TDM) are described: a sensitive, simple and rapid liquid chromatography-tandem mass spectrometry (LC-MS/MS) method to quantify isoniazid, ethambutol and pyrazinamide and an interlaboratory proficiency testing programme that enables laboratories to externally validate their bioanalysis methods for first-line and two second-line anti-TB drugs. The programme alerted some laboratories to previously undetected problems, demonstrating the need for and utility of an ongoing quality control programme in this area of bioanalysis.

For a drug to be effective, both its action at the site of the disease process (pharmacodynamics) and the drug concentration over time in body fluids and tissues (pharmacokinetics) are of major importance. For the first-line anti-TB drugs, the area under the concentration-time curve (AUC) is the most important pharmacokinetic parameter [2]. Drug exposure may be influenced by different factors, such as concomitant food-intake, comorbidities, co-medication and intra-individual differences in pharmacokinetics [1]. Patients prone to low drug exposure are those with mal-absorption and gastro-intestinal disorders, patients suffering from drug-drug interactions and those with diabetes mellitus or HIV co-infection. More importantly, pharmacokinetic variability is the driver of drug resistance [2, 3]. In all these individuals, there is a rationale for TDM [1].

Apart from the above-mentioned external factors, the first-line anti-TB drugs themselves are also problematic [1]. The variability of rifampicin plasma drug concentrations over time is influenced by its auto-inducing capacity, lowering rifampicin exposure with 40% after 40 days when the induction is maximized [4]. Variability of isoniazid exposure is further influenced by N-acetyltransferase 2 (NAT2), which metabolizes isoniazid to non-hepatotoxic metabolites. Generally, slow acetylators exhibit higher isoniazid plasma concentrations than rapid acetylators [5]. In a randomized clinical trial, isoniazid dosing adjusted for NAT2 genotype resulted in reduced toxicity and less treatment failure [6]. Clearance of isoniazid, rifampicin and pyrazinamide is a metabolic process handled by liver enzymes. Altered or impaired hepatic function further complicates dosing of these drugs. It is rather difficult to quantify the metabolizing capacity of the liver, making TDM the only way to ascertain adequate dosing [1]. Three of the first-line anti-TB drugs, isoniazid, rifampicin and pyrazinamide, are potentially hepatotoxic [7] and more so if plasma concentrations increase [8]. TDM may therefore also prevent toxicity if performed timely [1].

Low anti-TB drug exposure has been associated with poor treatment outcome, with an almost nine-fold increase in treatment failure in patients with low drug exposure [3]. Low maximum concentration (C_{\max}) preceded acquired drug-resistance [3]. Although the data were not related to minimum inhibitory concentrations (MICs), they clearly support the need for TDM [1].

In Chapter 5a, we described the development of an optimal sampling procedure based on population pharmacokinetics to predict AUC_{0-24} of rifampicin. The study subjects we included were TB patients, either participating in a pharmacokinetic study [9] or patients that were admitted to the University Medical Center Groningen, Tuberculosis Centre Beatrixoord, Haren, The Netherlands. These two groups of patients represent a rather diverse population; as for instance rifampicin was ingested on an empty stomach in the pharmacokinetic study and with a light breakfast in the Beatrixoord group. Possibly, patients in Beatrixoord reflect a more complicated group of TB patients as TDM of rifampicin is only performed based on a clinical indication and therefore, selection bias might be involved. A one-compartmental pharmacokinetic population model with first-order absorption and lag time was developed using observed rifampicin plasma concentrations from 55 patients. This study showed that rifampicin AUC_{0-24} in TB patients can be predicted with acceptable accuracy and precision using the developed population pharmacokinetic model with optimal sampling at time points 1, 3 and 8 h.

In a similar study, we developed a one-compartmental model with lag time for isoniazid using 36 concentration-time curves [10]. Optimal sampling using concentrations at 1, 3 and 8 h post dosing with r^2 0.96, root mean squared error 15.3% and prediction bias 3.3% was considered clinically suitable. Both estimated AUC_{0-24} using the one-compartmental model and estimated AUC_{0-24} using optimal sampling at time points 1, 3 and 8 h were highly correlated to the calculated AUC_{0-24} (Spearman correlation coefficient, 0.96; $p < 0.01$ and 0.95; $p < 0.01$ respectively) [10]. These optimal sampling studies facilitate obtaining an AUC and show that calculating AUC_{0-24} is possible with sufficient precision and accuracy. In future, in patient care there is no longer a need to obtain a full pharmacokinetic curve and this approach facilitates effective TDM.

For TB treatment, the time has come to move away from a 'one size fits all' approach [1]. We need individualized approaches with considerably more precision. In Chapter 6, we described a retrospective study in TB patients in which we investigated the correlation of clinical variables with the exposure of isoniazid and rifampicin. If size descriptors, such as body mass index (BMI), show a predictive relationship with drug exposure (AUC), than dose might be adjusted prior to start of treatment and TDM may not be necessary. Univariate analysis showed no association between isoniazid dose per total body weight (TBW) and exposure (adjusted

$R^2=0.008$, $P=0.232$). A small, but significant positive association was shown between rifampicin dose/TBW and exposure (adjusted $R^2=0.102$, $P=0.006$). Multiple linear regression analysis showed a significant, weak positive association of isoniazid AUC_{0-24} with the dose/TBW, BMI and elevated C-reactive protein (CRP) level (adjusted $R^2=0.162$, $P=0.010$). A significant, independent and positive association of rifampicin AUC_{0-24} was shown with the dose/TBW, gender, BMI and CRP level (adjusted $R^2=0.354$, $P<0.001$). Therefore, we conclude that 'dose doesn't matter'. To predict exposure of either drug, we will still have to perform TDM.

In drug-susceptible TB, breakpoints are used instead of actual MICs. Therefore, to date, we could only speculate on the pharmacokinetic/pharmacodynamic (PK/PD) parameter for determination of the efficacy of the treatment. We suggest to perform a trial in which exposure combined with susceptibility is tested for long-term outcome. This randomized clinical trial should explore the potential benefit of TDM in TB treatment. Standard treatment should be compared with TDM guided dosing in combination with MIC testing [1]. The study should be powered to detect both clinically and epidemiologically meaningful differences in relapse rate, acquired drug resistance or toxicity. TDM implementation in TB treatment need not necessarily increase cost [1]. Even in high TB-burdened, resource-poor countries TDM might at the end of the day prove cost-effective [1]. Local healthcare workers may be taught to take patient samples. Dried blood spot sampling (DBS) should be used because of considerable logistic and financial advantages involving easier sampling, storage and transportation, making TDM an attainable goal in remote, poorly resources areas [11].

Actual MICs of *M. tuberculosis* strains of patients on which we performed TDM (Chapter 6) are currently determined by the National Mycobacteria Reference Laboratory, National Institute for Public Health and the Environment, Bilthoven, the Netherlands. Combining these data with outcome, we will be able to determine the actual PK/PD parameter for efficacy.

In treatment-naïve TB patients who are starting on drug treatment, data on the influence of food intake on the pharmacokinetics were absent until recently. In Chapter 7, we performed the 'Fast-food trial', in which we quantified the influence of food on the pharmacokinetics of isoniazid, rifampicin, ethambutol and pyrazinamide in TB patients. A prospective randomized crossover pharmacokinetic study was conducted in 20 treatment-naïve adults with drug-susceptible TB, during the first three days of drug treatment. We investigated the influence of food on the (absolute) bioavailability and pharmacokinetics of the first-line anti-TB drugs. The high-carbohydrate meal influenced all pharmacokinetic parameters of isoniazid and rifampicin but not of ethambutol or pyrazinamide. Food decreased absolute bioavailability of isoniazid and rifampicin by approximately 15%. According to

regulatory guidelines [12], this is considered to be bioequivalent. However, this conclusion may be too conservative. A further reduction of drug exposure in patients prone to low drug exposure may actually increase the risk of poor treatment outcome [3, 6].

Besides the difference between the fed and fasted state, we were concerned about the very large ranges which were shown for AUC_{0-24} and absolute bioavailability. Between the highest and lowest value within a group, a factor 2.2, for fasted rifampicin, to 6.8, for fed isoniazid, was observed. In the optimal sampling studies and Chapter 6, we observed similar or even wider ranges [10]. Therefore, the effect of food intake contributed only partly to the large inter- and intra-individual pharmacokinetic variability [2] and it is again an argument to perform TDM.

Considering the importance of isoniazid in the first days of treatment and the fact that neither TDM nor pharmacokinetics will be performed on a daily basis, it seems worthwhile to investigate higher dosing of isoniazid for the first days, just as it is explored for rifampicin [13, 14]. Donald et al. did not find a higher EBA for doses over 300 mg but this may have been caused by a difference between slow and fast acetylators [15].

Physicians and pharmacists have used TDM in TB treatment if toxicity was suspected, or patients responded unfavourably. In this thesis, we have shown that TDM is ready for prime time. Next to possible upfront higher dosing of rifampicin and isoniazid, TDM is the way to go in our opinion. There are many situations in which TDM may make the difference between success and failure. Instead of working in the dark, with a gunshot approach, clinicians should switch on the light provided by TDM and support their clinical decisions with current technologies to hit their target with much more precision [1].

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